Prevalence of congenital anomaly syndromes in a Spanish gypsy population

M L Martínez-Frías, E Bermejo

Abstract

We analysed the sample of gypsies included in the Spanish Collaborative Study of Congenital Malformations (ECEMC), a hospital based, case-control study and surveillance system. Special emphasis was placed on the birth prevalence of recessive multiple congenital anomaly syndromes, comparing their frequency in the gypsy population with that observed among non-gypsies. We observed an increased prevalence of birth defects, mostly because of groups of children with patterns of multiple anomalies and with autosomal recessive syndromes. The latter were approximately seven times more frequent in gypsies than in non-gypsies. We also estimated the carrier frequency in both groups (gypsy and non-gypsy). We consider that the frequent occurrence of the conditions observed reflects the high rate of consanguineous couples among the Spanish gypsy population.

There are very few population studies on congenital defects among gypsies, and information on congenital anomalies in this ethnic group comes mainly from family reports or sporadic cases.[1-3] In general, there are few scientific reports about other health aspects of the gypsy population,[4] and most of them are on blood groups,[5-8] PKU,[9-11] congenital glaucoma,[12-14] and other genetic disorders.[9]

Here we present an analysis of the prevalence of multiple congenital anomaly (MCA) syndromes, with special emphasis on recessive disorders, observed in a Spanish population of gypsies identified through the Spanish Collaborative Study of Congenital Malformations (ECEMC). We also estimate the rate of consanguinity and compare it with that in the non-gypsy population of the ECEMC.

Material and methods

The ECEMC is a hospital based, case-control study and surveillance system. All infants born in about 51 collaborating hospitals all over Spain are examined by collaborating physicians during the first three days of life to identify major and minor congenital defects. Photographs, radiographs, and necropsy reports are included when available. For each case, the next non-malformed infant of the same sex born in the same hospital is selected as a control. The physicians interview the mothers of cases and controls to gather information on obstetric data, prenatal exposures, and family history, including a question about the race of the parents and the four grandparents of the child. Detailed description of the ECEMC has been published elsewhere.[15-17]

From April 1976 to September 1990, the ECEMC surveyed a total population of 830 883 liveborn infants. Of these, 16 736 were malformed and 16 576 were selected as controls. Race was specified in 14 083 malformed

Table 1 Study population (April 1976 to September 1990).

	Gypsies			Non-gypsies			
	No	%	Per 1000 liveborns	No	%	Per 1000 liveborns	Total
Malformed children	273	1·94	21·1*	13 810	98·06	16·9	14 083
Controls	218	1·56	—	13 791	98·44	—	14 009
Total liveborns	12 962†		—	817 921		—	830 883

* $\chi^2_1 = 5{\cdot}76$; $p = 0{\cdot}01$.
† Estimated from the distribution among controls.

Table 2 Proportion of consanguineous couples.

		Gypsies		Non-gypsies	
		Malformed infants*	Control infants†	Malformed infants	Control infants
Consanguineous	No	97	61	308	210
	%	(36·9)	(29·3)	(2·3)	(1·5)
Non-consanguineous	No	166	147	13 324	13 400
	%	(63·1)	(70·7)	(97·7)	(98·5)
Consanguinity not known	%	10	10	178	181
Total		273	218	13 810	13 791

χ^2 comparing gypsies and non-gypsies.
* For malformed infants (gypsies *v* non-gypsies) $\chi^2_1 = 1081$, $p < 0{\cdot}000001$.
† For control infants (gypsies *v* non-gypsies) $\chi^2_1 = 808$, $p < 0{\cdot}000001$.

INSALUD, Hospital Universitario San Carlos y ECEMC, Facultad de Medicina, Universidad Complutense, Madrid, Spain.
M L Martínez-Frías
E Bermejo

Correspondence to Dr Martínez-Frías, ECEMC, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain.

Received 19 February 1991.
Revised version accepted 15 October 1991.

Table 3 Malformed infants in gypsy and non-gypsy populations by clinical presentation.

	Gypsies		Non-gypsies		RR for gypsies
	No	%	No	%	
Isolated defects	198	72·53	10 725	77·66	0·93
Multiple defects	50	18·31	1560	11·30	1·62
Syndromes	25	9·16	1525	11·04	0·83
Total	273	100	13 810	100	—

$\chi^2_2 = 13{\cdot}31$, $p = 0{\cdot}001$.
RR = the proportion among gypsies divided by the proportion among non-gypsies.

Table 4 Types of syndrome identified in gypsy and non-gypsy populations.

	Gypsies		Non-gypsies		RR for gypsies
	No	Per 1000	No	Per 1000	
Chromosomal	12	0·93	1133	1·38	0·68
Mendelian	12	0·93	238	0·29	3·21
Recessive syndromes	10	0·77	92*	0·11	7·00
Dominant syndromes	1	0·08	86	0·10	0·80
Other	1	0·08	65	0·08	1·00
Unknown aetiology	1	0·08	76	0·09	0·89
Environmental	0	—	73	0·09	—
Total	25	1·93	1525	1·86	1·04

For all syndromes $\chi^2_3 = 19{\cdot}49$, $p = 0{\cdot}0002$. For mendelian syndromes $\chi^2_2 = 9{\cdot}86$, $p = 0{\cdot}007$.
* We have included two cases of albinism and three cases of epidermolysis bullosa although we do not know the type. If some of these syndromes were not the recessive type, the difference would increase the relative risk for gypsies.

Table 5 Types of recessive syndrome identified in gypsy and non-gypsy populations (prevalence per 10 000).

	Gypsies		Non-gypsies		Gypsies/ non-gypsies (RR)
	No	Per 10 000	No	Per 10 000	
Albinism	4	3·09	2	0·02	154·5
Epidermolysis bullosa	2	1·54	9	0·11	14·0
Bowen-Conradi syndrome	1	0·77	0	—	—
Jarcho-Levin syndrome	1	0·77	3	0·04	19·3
Meckel syndrome	1	0·77	8	0·10	7·7
Smith-Lemli-Opitz syndrome	1	0·77	4	0·05	15·4
Other recessives	0	—	66	0·81	—
Total	10	7·71	92	1·12	6·9

Table 6 Proportion of consanguineous couples among the different types of recessive syndrome identified in gypsy and non-gypsy populations.

	Consanguineous couples					
	Gypsies			Non-Gypsies		
	No	Yes	%	No	Yes	%
Albinism	3	1	25	2	0	0
Epidermolysis bullosa	0	2	100	7	2	22·2
Bowen-Conradi syndrome	0	1	100	0	0	—
Jarcho-Levin syndrome	1	0	0	3	0	0
Meckel syndrome	0	1	100	7	1	12·5
Smith-Lemli-Opitz syndrome	0	1	100	4	0	—
Other recessives	0	0	—	60	6	9·1
Total	4	6	60	83	9	9·8

Table 7 Carrier frequency for recessive syndromes identified in gypsies compared with non-gypsies.

	Gypsies	Non-gypsies	Times more frequent among gypsies
Albinism	1/29	1/320	11·0
Epidermolysis bullosa	1/41	1/150	3·7
Bowen-Conradi syndrome	1/57	—	—
Jarcho-Levin syndrome	1/57	1/216	3·8
Meckel syndrome	1/57	1/160	2·8
Smith-Lemli-Opitz syndrome	1/57	1/226	4·0

children and in 14 009 controls. For the purposes of this study, we considered that a child was a gypsy if at least one of the four grandparents was a gypsy.

Since the ECEMC is a case-control study, we used the percentage of gypsies observed among the control children (1·56%) to estimate the number of gypsies among the total number of liveborn infants registered during the study period (table 1).

Results

The study sample of gypsies and non-gypsies is shown in table 1. The total number of gypsies estimated from the proportion among the controls is 12 962, which represents 1·56% of the 830 883 liveborn infants examined during the study period. We can also observe from table 1 that the prevalence of malformed children among gypsies is higher ($p = 0{\cdot}01$) than among non-gypsies. Table 2 shows the proportion of consanguineous couples in the two study samples. Among the malformed gypsy children, 36·9% of the parents were consanguineous compared with 29·3% among the non-malformed gypsy infants. In the non-gypsy sample, the proportion of consanguineous parents was much lower (2·3% of the malformed infants and 1·5% of the controls). In other words, the proportion of consanguineous couples in the gypsy population is 16 and 19·5 times that of malformed and non-malformed non-gypsy infants, respectively.

Table 3 shows the distribution of malformed children by clinical presentation. The relative risk for gypsies (that is, the proportion among gypsies divided by the proportion among non-gypsies) shows that children with multiple defects are more frequent among gypsies than among non-gypsies. Table 4 presents the different types of syndrome. Those of genetic aetiology are 3·21 times more frequent in the gypsy than in the non-gypsy population. Also in table 4, it can be seen that recessive syndromes are about seven times more frequent among gypsies; this difference is statistically significant ($p < 0{\cdot}00001$). The gypsy sample, who only make up 1·56% of the total liveborn population, accounts for 10% of the recessive syndromes detected in the total population surveyed by the ECEMC. The syndromes identified among gypsies were: chromosomal abnormalities (12 cases, 10 of which were trisomy 21), thanatophoric dwarfism (1), and pseudotrisomy 13 syndrome (1). The recessive syndromes are listed in table 5. Because the Spanish public health system covers over 99% of the population, we do not consider that the gypsies who have their children in hospital represent a biased sample.

Table 5 shows the prevalence figures for the different types of recessive syndrome in the two groups. All of them are more frequent in the gypsies, especially albinism, which is 154.5 times more frequent among gypsies than non-gypsies. Table 6 shows the recessive syndromes and their relationship with parental consanguinity, comparing the gypsy and non-gypsy samples. The carrier frequency for the

recessive syndromes observed in the two groups is shown in table 7.

Discussion

The gypsies constitute an isolated group in all countries where they have settled since their original emigration from India, maintaining their language, customs, and culture over time. Compared to the Amish or other genetic isolates, there are no population studies on multiple congenital anomaly syndromes among gypsies, only case reports.[1-3 18] As far as we know, this is the first study on MCA syndromes in a gypsy population.

As we have shown, the suspected, albeit usually unquantified, high proportion of consanguineous couples is important. In this study, the proportion of consanguineous couples in the gypsy population is 16 to 19·5 times that in non-gypsies. This level of parental consanguinity leads to a high proportion of homozygotes for recessive conditions in the offspring and, consequently, to a high rate of recessive syndromes. We have estimated that the rate of well known recessive syndromes among gypsies is seven times that among non-gypsies. It is also interesting to note the higher frequency of children with multiple congenital anomalies among gypsies. This suggests that this group could include unidentified recessive conditions. This and other aspects of the prevalence of congenital defects among the gypsy populations will be studied separately.

Among the different types of autosomal recessive syndrome, we observed two children with epidermolysis bullosa and four infants with albinism. We also identified one consanguineous family that is not included in the tables because the proband had cleft lip and palate, but had an older sib with albinism. We do not know the type of albinism, but all five cases must have the same autosomal recessive type, because all the families share the same surname although in only two of the five couples was consanguinity recognised.

In Spain, each person uses two surnames; the first is the father's first surname and the second is the mother's first surname (women do not change their surnames when married). Most people know their four surnames or even eight (the four of the father and the four of the mother). This system permits a detailed analysis of kinship. In fig 1, we indicate with a letter the different surnames of the five families with albinism. It can be seen that they share some of the surnames and that we can trace all of the families by one of them (surname A). Moreover, when we analysed the other affected relatives, they correspond to one, at least, of the other four families in the study.

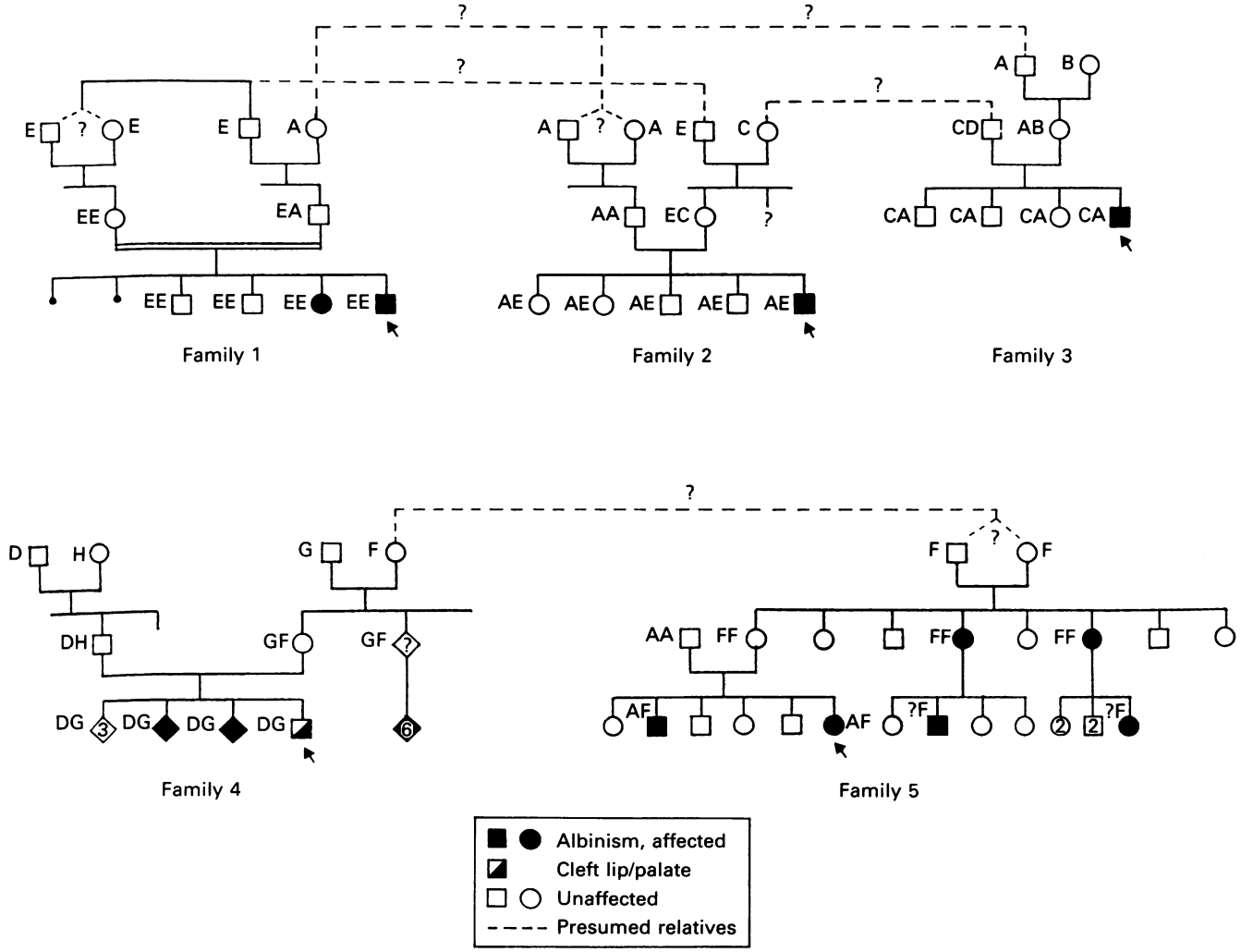

Figure 1 Gypsy families with albinism. A, B, C, D, E, F, G: surnames abbreviated for confidentiality.

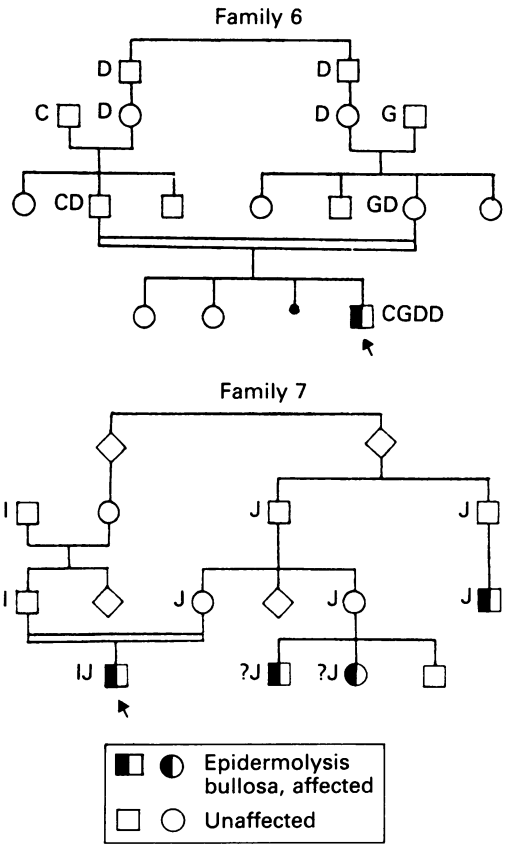

Figure 2 Gypsy families with epidermolysis bullosa. C, D, G, I, J: surnames.

The two cases with epidermolysis bullosa were born to consanguineous couples (fig 2). One of them came from Portugal and the surnames are different. The family from Spain presented with epidermolysis bullosa, dystrophic type. We do not know the type in the other family, but it might be one of those with recessive inheritance. In all seven families, the four grandparents were gypsies.

Like other isolated populations, gypsies have particular cultural characteristics, one of the most important of which is the high level of endogamy, with subsequent high rate of consanguinity. This transforms this population into a high genetic risk group because it results in unions of carriers of some recessive conditions. This should be taken into consideration in genetic counselling and health care planning.

We think that the frequent occurrence of the recessive conditions observed in our sample of the gypsy population simply reflects the high rate of consanguineous marriage. However, it is conceivable that these genes could occur with high frequency in the gypsies of other countries. More information on this isolated ethnic group will be important to learn more about their genetic constitution.

This work was supported by the Real Patronato de Prevención y de Atención a Personas con Minusvalías, and by a grant from the Dirección General de Planificación Sanitaria, Ministerio de Sanidad y Consumo of Spain. We would like to thank the collaborating physicians of the ECEMC who collected the information.

1 Váradi V, Szabó L, Papp Z. Syndrome of polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation in endogamic gypsies. *J Med Genet* 1980;**17**:119–22.
2 Bellyei A, Czeizel A. A higher incidence of congenital structural talipes equinovarus in gipsies. *Hum Hered* 1983;**33**:58–9.
3 Malpuech G, Demeocq F, Palcoux JB, Vanlieferinghen P. A previously undescribed autosomal recessive multiple congenital anomalies mental retardation syndrome with growth failure, lip/palate cleft(s), and urogenital anomalies. *Am J Med Genet* 1983;**16**:475–80.
4 Thomas JD. Gypsies and American medical care. *Ann Intern Med* 1985;**102**:842–5.
5 Bartsocas CS, Karayanni C, Tsipouras P, Baibas E, Bouloukos A, Papadatos C. Genetic structure of the Greek Gypsies. *Clin Genet* 1979;**15**:5–10.
6 Beckman L, Takman J, Arfors KE. Distribution of blood and serum groups in Swedish Gypsy population. *Acta Genet Stat Med* 1965;**15**:134–9.
7 Bernasovsky I, Suchy J, Bernasovska K, Vargova T. Blood groups of Roms (Gypsies) in Czechoslovakia. *Am J Phys Anthropol* 1976;**45**:277–80.
8 Harper PS, Williams EM, Sunderland E. Genetic markers in Welsh Gypsies. *J Med Genet* 1977;**14**:177–82.
9 Williams EM, Harper PS. Genetic study of Welsh gypsies. *J Med Genet* 1977;**14**:172–6.
10 Forrai G, Tauszik T, Tauszik N, *et al.* A high incidence of PKD in a large geographic area of South-Western Hungary: a medical genetic study. In: *Genetics of kidney disorders*. New York: Alan R Liss, 1989:89–94.
11 Tyfield LA, Meredith AL, Osborn MJ, Harper PS. Identification of haplotype pattern associated with the mutant PKU allele in the Gypsy population of Wales. *J Med Genet* 1989;**26**:499–503.
12 Gencík A, Gencíkova A, Ferák V. Population genetic aspects of primary congenital glaucoma. I. Incidence, prevalence, gene frequency and age of onset. *Hum Genet* 1982;**61**:193–7.
13 Ferák V, Gencík A, Gencíkova A. Population genetic aspects of primary congenital glaucoma. II. Fitness, parental consanguinity, founder effect. *Hum Genet* 1982; **61**:198–200.
14 Gencíkova A, Gencík A. Congenital glaucoma in Gypsies from Slovakia. *Hum Hered* 1982;**32**:270–3.
15 Martínez-Frías ML. Clinical manifestation of prenatal exposure to Valproic acid using case reports and epidemiologic information. *Am J Med Genet* 1990;**37**:277–82.
16 Martínez-Frías ML, Frías JL, Salvador J. Clinical/epidemiological analysis of malformations. *Am J Med Genet* 1990;**35**:121–5.
17 Martínez-Frías ML, Salvador J, Prieto L, Zaplana J. Epidemiological study of gastroschisis and omphalocele in Spain. *Teratology* 1984;**29**:377–82.
18 Courtens W, Broeckx W, Ledoux M, Vamos E. Oculocerebral hypopigmentation syndrome (Cross syndrome) in a Gipsy child. *Acta Paediatr Scand* 1989; **78**:806–10.